REMARKS/ARGUMENTS

After entry of this amendment, claims 69-72 and 75-106 are pending, claim 69 having been amended, claims 76-78 and 93-96 having been withdrawn as being drawn to a non-elected species, and claims 1-68 and 73-74 having been previously canceled.

I. Status of the Claims

The Examiner states that claims 93-96 are withdrawn from consideration as being drawn to a non-elected species. Claim 93, directed to a pharmaceutical composition comprising mC10 and an antigen wherein the chemokine and antigen are linked, is drawn to the elected species. Applicants respectfully request that the Examiner considers claim 93 along with claims 69-72, 75, 79-92 and 97-106.

Claim 69 is amended to introduce "chemokine 2" for clarity. Support is provided in the specification, e.g., at page 59, lines 11-18. No new matter is added by this amendment.

II. Formal Matters

In the instant Final Office Action, the Examiner states that the amendment filed August 17, 2005 will not be entered. Applicants note that the paper filed on August 17, 2005 was not a Supplemental Amendment, but, rather, was a Request for Corrected Filing Receipt. Attached thereto was a copy of the Preliminary Amendment and Response to Restriction Requirement, originally filed March 8, 2004, which was merely provided as a courtesy copy in support of the request.

III. The Claimed Invention

The presently claimed invention is directed to pharmaceutical compositions comprising a chemokine, either mC10 (or C10) or vMCK-2 (or MCK-2), and an antigen. Applicants have shown that such pharmaceutical compositions are useful for enhancing an immune response to the antigen in primates (i.e., Rhesus monkey). Examples 3 to 5 show that

mC10 and vMCK-2 cause unexpectedly high levels of infiltration of various antigen-presenting cells ("APCs"; e.g., dendritic cells and mononuclear cells) at the site of injection in Rhesus monkeys. Example 6 shows that mC10 and vMCK-2 significantly augment the immune response (i.e., antibody response) to a co-injected antigen in Rhesus monkeys. These activities of mC10 and vMCK-2 are unexpected and are particularly surprising because there is no human homolog of mC10 nor a homolog of vMCK-2 produced by a virus that infects humans.

IV. Claim Rejections

Claims 89-92 and 97-106 are rejected as being unpatentable over Kedar et al., *Adv. Cancer Res.* 59:245-322, 1992 ("Kedar") in view of Bystryn, WO 98/33520 ("Bystryn") and Mohamadzadeh et al., *Arch. Dermatol. Res.* 289:435-439, 1997 ("Mohamadzadeh") and Orlofsky et al., *Cytokine* 12:220-228, 2000 ("Orlofsky").

The Examiner cites Kedar as discussing cancer immunotherapy methods. The Examiner cites Kedar as allegedly teaching: (1) the antigenicity of a tumor and capacity to mobilize a T-cell response are required for successful immunotherapy; (2) infiltrating macrophage, neutrophils and eosinophils, which are present in regressing tumors, are mobilized by lymphokines released from antigen-specific T-cells; (3) the infiltrating cells contribute to the therapeutic effect; (4) stealth liposomes can achieve prolonged circulation time and enhanced accumulation in tumors; (5) administration of biological modifiers such as cytokines by encapsulation in liposomes bypasses the need for continuous infusion or frequent bolus administration of the cytokine or other biological response modifier; (6) tumor antigens encapsulated in liposomes can improve immunogenicity of the tumor antigen in humans; (7) administration of the tumor antigen together with cytokines and improved adjuvants increases anti-tumor efficacy in experimental animals; and (8) treatment with combinations of subtoxic doses of cytokines with different activities may improve therapeutic index. The Examiner acknowledges that Kedar does not specifically teach mC10 as a biological response modifier, or an encapsulated liposome comprising a chemokine, adjuvant and a tumor antigen.

The Examiner cites Bystryn as discussing pH sensitive liposomes. The Examiner cites Bystryn as allegedly teaching: (1) liposome encapsulated vaccines containing immunomodulators; (2) the administration of encapsulated vaccines by various routes; and (3) pH sensitive liposomes are taken up by APCs.

The Examiner cites Mohamadzadeh as discussing mC10. The Examiner cites Mohamadzadeh as allegedly teaching that dendritic cells and Langerhan's cells are sources of mC10, which recruits T-cells, and cytokines, which are involved in the initiation of inflammatory events, and can process and present protein antigens and induce primary T-cell responses.

The Examiner cites Orlofsky as discussing mC10. The Examiner cites Orlofsky as allegedly teaching: (1) murine chemokine mC10 modulates immune reactions of the Th2 type; (2) subsequent development of the Th2 response is ineffective in suppressing mC10 expression; (3) mC10 is chemotactic for macrophages and T and B lymphocytes; and (4) mC10 either maintains modes of cellular inactivity previously initiated by transient chemokines or specifically attracts one or more T-cell subsets.

The Examiner alleges that it would have been obvious to use mC10 as an immunomodulator in the stealth liposomes taught by Kedar and to combine mC10 with a tumor antigen, an additional chemokine and an adjuvant in the liposomes. The Examiner alleges that the skilled artisan would have been motivated by the teachings of Kedar, on accumulation of stealth liposomes at the tumor site, Orlofsky, on maintenance of the Th2 response by mC10, and Orlofsky and Mohamadzadeh, on recruitment of T cells and cytokines involved in the inflammatory response.

The motivation asserted by the Examiner to combine liposome encapsulated mC10 with a tumor antigen is that Kedar teaches that encapsulation of tumor antigens within liposomes can improve immunogenicity. The motivation asserted by the Examiner to combine mC10 with an additional chemokine is to exert an additive or synergistic effect. The motivation

asserted by the Examiner to prepare sterile preparations of the liposome encapsulated pharmaceuticals is to preserve the shelf life of the pharmaceuticals and to prevent contamination.

Applicants respectfully traverse this rejection.

Kedar reviews cancer immunotherapy and provides a variety of suggestions to improve the efficacy and safety of cancer immunotherapy. In particular, Kedar discusses the use of a variety of cytokines, alone or in combination with other biological response modifiers, antigens and/or immune cells, in cancer immunotherapy in humans and in animal model systems. Bystryn discusses vaccine compositions having an antigen, an immunomodulator, and a pH sensitive liposome as carrier. Bystryn lists several cytokines among immunomodulators that enhance and amplify immune responses induced by an antigen. Mohamadzadeh discusses dendritic cells and Langerhan's cells, which are cellular sources of C10, for the recruitment of T cells, and cytokines, which are involved in initiating inflammatory events. Orlofsy discusses the potential role of mC10 in Th2 immune reactions. None of these references, however, discuss or even mention the use of chemokines generally, or mC10 specifically, in cancer immunotherapy.

Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because there is no motivation to make the specific combination of references that would lead to the presently claimed invention. "To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (BPAI 1993).

Here, the asserted motivation to combine the references is entirely predicated on the Examiner's presumption that the skilled artisan would have recognized that Kedar meant to include chemokines among cytokines useful for cancer immunotherapy. As discussed in detail

below, while agreeing that a chemokine is a class of cytokine, there is nothing in Kedar that supports the Examiner's presumption. It is respectfully submitted that the Examiner has failed to provide any objective evidence or reasoning why the skilled artisan at the time of the instant application was filed would have considered that Kedar's discussion of cytokines was meant to include chemokines, in general, or mC10, in particular.

The Examiner's rebuttal of the argument set forth in the response filed September 7, 2004, namely, that Kedar provides no motivation for combining references which teach cytokines as opposed to chemokines, fails to address the underlying issue. Whether or not the skilled artisan would understand that a chemokine is a pro-inflammatory cytokine and thus encompassed in the family of cytokines, does not provide any objective evidence that Kedar intended to include the subgenus of cytokines, chemokines, among the larger genus of cytokines considered useful for cancer immunotherapy. As detailed below, a careful examination of the Kedar reference clearly demonstrates that the authors did not at all contemplate chemokines when considering the past, present and future of cancer immunotherapy.

First, Kedar specifically mentions many cytokines, including IL-2, IFNγ, IFNα, IFNβ, TNFα, IL-1, IL-4, IL-6, IL-7 and IL-10, and several classes of cytokines potentially useful for cancer immunotherapy, including lymphokines, interleukins and colony stimulating factors; however, chemokines are not mentioned. In fact, Kedar does not even once mention a single chemokine in almost 50 pages of reviewing methods of cancer immunotherapy.

Second, in the first full paragraph on page 258 of Kedar, it is stated that "over 20 cytokines (among them 12 interleukins) are known and functionally defined." At the time Kedar was published in 1992, more than a dozen functionally defined chemokines were known in the literature (see attached pages 822-826 of Fundamentals of Immunology, 3rd Edition, Paul, WE., ed., Raven Press, New York, 1993). Thus, it is apparent that Kedar did not include chemokines among the number of known and functionally defined cytokines.

Third, in the last full paragraph on page 258 of Kedar, it is stated that "cytokines can be useful in cancer treatment by (1) exerting direct effects on the tumor (cytolysis, cytostasis, vasculature damage, terminal differentiation, (2) enhancing the expression of MHC antigens, cell adhesion molecules, and other surface moieties on the tumor cells including tumor-associated antigens, (3) recruiting, expanding, and stimulating endogenous effector cells, and (4) maintaining and even enlarging adoptively transferred lymphocyte populations." By the time the Kedar article was written, chemokines were well-known in the art as secreted proteins with chemotactic activity (see attached pages 822-826 of Fundamentals of Immunology, 3rd Edition, Paul, WE., ed., Raven Press, New York, 1993). Except for recruiting activity, none of the above cytokine activities useful for cancer treatment were known to be activities associated with chemokines.

Based on the foregoing, it is clear that Kedar was referring to cytokines in the narrower sense, including cytokines specifically mentioned therein or their equivalents, and not in the broader sense of the entire genus of cytokines, including the subgenus, i.e., chemokines, which lack the anti-tumor activities that the reference ascribes to cytokines.

The various sources of motivation asserted by the Examiner to combine the references are no more that the reasons for performing the individual methods discussed in the references. The first source of motivation for combining the references alleged by the Examiner (i.e., Kedar's discussion of the use of cytokines in cancer immunotherapy in general, and the advantages of using tumor antigens and cytokines encapsulated within liposomes for improving immunogencity in particular) is the reason for doing: (1) what was already being done, namely, using cytokines for cancer immunotherapy; and (2) what Kedar proposes, namely, encapsulating a tumor antigen and a cytokine or a combination of cytokines. The alleged motivation does not point to any specific modification of Kedar's teaching. As discussed above, Kedar does not teach or suggest the possibility of using a chemokine in place of a cytokine. The alleged motivation particularly would not have impelled the skilled artisan to replace a cytokine with any chemokine and in particular mC10, alone or in combination with another chemokine.

The second source of motivation alleged to support combination of the references (i.e., Bystryn's using pH sensitive liposomes to encapsulate an antigen and an immunomodulator) is likewise the reasons for doing what Bystryn was already doing, namely, using pH sensitive liposomes to improve vaccine administration and immune responses. The alleged motivation does not point to any particular modification of Kedar's or Bystryn's teaching and particularly would not have impelled the skilled artisan to use chemokines in general, or mC10 in particular, in place of cytokines in vaccine preparations. Bystryn does not teach or suggest that chemokines are to be considered among those immunomodulators useful in vaccine preparations.

The third source of motivation alleged to support combination of the references (i.e., Mohamadzadeh's teaching of dendritic cells and Langerhan's cells, which are cellular sources of chemokines, including mC10, which recruit T cells, and cytokines, which are involved in the initiation of inflammatory events) is likewise deficient. The alleged motivation is merely the reasons for performing studies discussed by Mohamadzadeh, namely, characterizing dendritic cells as antigen-presenting cells. The alleged motivation would not have impelled the skilled artisan to replace cytokines with chemokines in vaccine preparations.

The fourth source of motivation alleged to support combination of the references (i.e., Orlofsky's teaching of the possible activities of mC10 in maintaining the Th2 response and recruitment of T cells) is likewise deficient. The alleged motivation is merely the reasons for performing studies discussed by Orlofsky, namely, characterizing the role of mC10 in regulating immune reactions of the Th2 type. The alleged motivation would not have impelled the skilled artisan to replace cytokines with chemokines in vaccine preparations.

Therefore, Bystryn, Mohamadzadeh and Orlofsky all fail to compensate for the deficiency in Kedar, namely, the lack of any teaching, suggestion or motivation to replace the cytokine with the chemokine mC10 in pharmaceutical compositions comprising a tumor antigen.

Not only is there no motivation to combine the references in the manner alleged by the Examiner, the results obtained by Applicants were surprising and unexpected. The

Examiner's rebuttal of the argument set forth in the response filed September 7, 2004, namely, that the skilled artisan would not have reasonably expected a murine chemokine (mC10) that has no human homolog to trigger primate APCs, fails to adequately address the issue. The Examiner refers to Saederup, which discusses the ability of a mouse virus chemokine (vMCK-1) to exert effects on human cells, and then states "it appears that chemokines can exert chemoattractant activity is heterologous (sp.) hosts. Further, the instant claims are product claims and therefore not limited by intended use in humans." The Examiner's response is not well taken.

First, the Examiner failed to provide any objective evidence or reasoning that the skilled artisan would have reasonably expected mC10 to trigger primate APCs. Given that the majority of chemokines identified at the time of the instant application showed strict species specificity, it would have been unreasonable to expect murine chemokines in general, or mC10 in particular, to exert chemoattractant activity in primates. Applicants' finding that mC10 could nonetheless induce and augment an immune response in primates was unexpected and particularly surprising because there is no human homolog to mC10.

Second, the Examiner's discussion of the ability of the mouse virus chemokine vMCK-1 to exert effects on human cells has little or no bearing on whether it is reasonable to expect mC10 to exert chemoattractant activity in primates. This single observation would not have provided a sufficient basis for the skilled artisan to reasonably expect that the experience with a mouse virus chemokine could be translated to the murine chemokine, mC10.

Third, although the instant product claims are not limited by an intended use in humans, it is entirely proper for the Examiner to consider the advantages of an invention when evaluating its obviousness. The Federal Circuit has stated that "advantages...do not properly belong in the claims, the sole function of which is to point out distinctly the process, machine, manufacture or composition of matter which is patented...not its advantages." *Preemption Devices v. Minnesota Mining & Manufacturing Co.*, 732 F.2d 903, 907 (Fed. Cir. 1984). The Federal Circuit added that "it is entirely proper, nevertheless, in evaluating nonobviousness...to

take into account advantages directly flowing from the invention patented." *Id.* Here, the presently claimed pharmaceutical compositions comprising mC10 and a tumor antigen may be used for vaccine administration to humans. The suitability of the composition to administer to a human is an inherent property of the composition irrespective of whether it is actually administered to a human. This advantage naturally follows from what is claimed, and it is entirely appropriate to consider it as evidence of nonobviousness.

The Federal Circuit has emphasized the requirement for evidence of particularized motivation as a safeguard against the "tempting but forbidden zone of hindsight." *In re Dembiczak*, 50 USPQ2d 1614, 1616 (Fed. Cir. 1999). As discussed above, the various sources of motivation asserted by the Examiner are not particularized to the claimed invention but simply the reasons for performing the individual studies and methods discussed in the cited references. In these circumstances, the proposed manner of combination of references, which requires that the skilled artisan recognize that a cytokine can be replaced by a specific chemokine, mC10, in the absence of any teaching or suggestion that the subgenus of chemokines were considered to be equally useful as the specified cytokines in cancer immunotherapy, appears to be the result of impermissible hindsight.

Based on the foregoing, Applicants respectfully request that the rejection of claims 89-92 and 97-106 as being unpatentable over Kedar in view of Bystryn, Mohamadzadeh and Orlofsy be withdrawn.

Claims 69-72, 79-92 and 97-106 are rejected as being unpatentable over Kedar in view of Bystryn and Saederup et al., *Proc. Natl. Acad. Sci. USA* 96:10881-10886, 1999 ("Saederup").

The Examiner cites Kedar as discussing cancer immunotherapy methods, and Bystryn as discussing pH sensitive liposomes, as described above.

The Examiner cites Saederup as discussing vMCK-2. The Examiner cites Saederup as allegedly teaching: (1) vMCK-1 /vMCK-2 are responsible for promoting host leukocyte chemotaxis and may be responsible for attracting monocytes and macrophages; (2) vMCK-1 and vMCK-2 have the same chemokine domain, but vMCK-2 contains an additional 199 amino acid sequence; (3) vMCK-1 can recruit and activate monocytess or macrophages; and (4) an vMCK-1/vMCK-2 mutant cannot sustain an inflammatory response, consistent with the role of maintaining monocyte migration.

The Examiner alleges that it would have been obvious to use vMCK-2 as an immunomodulator in the stealth liposomes taught by Kedar and to combine vMCK-2 with a tumor antigen, an additional chemokine and an adjuvant in the liposomes for administration to patients.

The motivation asserted by the Examiner is that Kedar teaches the accumulation of stealth liposomes at the tumor site and the therapeutic effect associated with the recruitment of monocytes and macrophages to the tumor site, and Saederup teaches recruitment of monocytes and macrophages by vMCK-1/vMCK-2. According to the Examiner, the skilled artisan would conclude that vMCK-1 and vMCK-2 can be used interchangeably based on the teachings of Saederup.

The motivation asserted by the Examiner to combine vMCK-2 with an additional chemokine is to exert an additive or synergistic effect. The motivation asserted by the Examiner to further encapsulate the adjuvant is the teachings of Bystryn. The motivation asserted by the Examiner to prepare sterile preparations of the liposome encapsulated pharmaceuticals is to preserve the shelf life of the pharmaceuticals and to prevent contamination.

Applicants respectfully traverse this rejection.

The teachings of Kedar and Byrstryn are discussed above. Saederup teaches that vMCK-1 acts on human macrophage cells and that vMCK-1/vMCK-2 may be responsible for

attracting monocytes or macrophages to the site of viral infection. None of these references, Kedar, Bystryn or Saederup, however, discuss or even mention the use of chemokines generally, or vMCK-2 specifically, in cancer immunotherapy.

Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because there is no motivation to make the specific combination of references that would lead to the presently claimed invention. Again, the asserted motivation to combine the references is entirely predicated on the Examiner's presumption that the skilled artisan would have recognized that Kedar meant to include the subgenus of chemokines among larger genus of cytokines useful for cancer immunotherapy. As discussed in detail above, there is nothing in Kedar that supports the Examiner's presumption, and after careful examination of Kedar it is clear that the authors did not contemplate chemokines in general, or vMCK-2 in particular, when considering the use of cytokines in cancer immunotherapy.

Again, the various sources of motivation asserted by the Examiner to combine the references are no more that the reasons for performing the individual methods discussed in the references. The first and second sources of motivation for combining the references alleged by the Examiner (i.e., Kedar and Bystryn) are discussed above. A further motivation asserted by the Examiner is that Kedar teaches the therapeutic effect associated with recruitment of monocytes and macrophages to the tumor site. Applicants respectfully submit that the Examiner has taken the teachings of Kedar out of context. On pages 253-254 of Kedar, it is stated that "regressing tumors are often infiltrated by macrophages, neutrophils and eosinophils and that "BRM-stimulated nondiscriminative effector cells, such as macrophages and NK/LAK cells, may contribute to the therapeutic effect." A more straightforward interpretation of the above passages is that the therapeutic effect of cytokines may be due to stimulation of such macrophages that have already at the tumor site. Thus, there would be no need to administer a chemokine to attract macrophages that have already infiltrated the tumor, whereas it would be desirable to administer a cytokine to stimulate or activate the infiltrated cells. The alleged motivation does not point to any particular modification of Kedar's or Bystryn's teaching, and particularly would not have

impelled the skilled artisan to use chemokines in general, or vMCK-2 in particular, in place of cytokines in vaccine preparations. Neither Kedar nor Bystryn teach or suggest that a chemokine is to be considered among those cytokines or immunomodulators useful in vaccine preparations.

The third source of motivation alleged to support combination of the references (i.e., Saederup's teaching of recruitment of monocytes and macrophages by vMCK-1/vMCK-2 and the alleged interchangeably between vMCK-1 and vMCK-2) does not compensate for the deficiency in Kedar. As discussed in detail below, the skilled artisan would not have reasonably expected the activities of vMCK-1 and vMCK-2 to be interchangeable. Accordingly, the alleged motivation is merely the reasons for performing studies to further investigate the activities of vMCK-1 and vMCK-2. The alleged motivation would not have impelled the skilled artisan to replace cytokines with chemokines, in particular vMCK-2, in the vaccine preparations.

Therefore, Bystryn and Saederup both fail to compensate for the deficiency in Kedar, namely, the lack of any teaching, suggestion or motivation to replace the cytokine with the chemokine vMCK-2 in pharmaceutical compositions comprising a tumor antigen.

Not only is there no motivation to combine the references in the manner alleged by the Examiner, the results obtained by Applicants were surprising and unexpected. The Examiner's rebuttal of the argument set forth in the response filed September 7, 2004, namely, that the skilled artisan would not have reasonably expected a murine viral chemokine (vMCK-2), which has no human virus homolog, to trigger primate APCs, fails to adequately address the issue. The Examiner refers to Saederup, which discusses the ability of a mouse virus chemokine (vMCK-1 and vMCK-2) to exert effects on human cells, and then simply points out that the claims are product claims and thus not limited by intended use. The Examiner's response is not well taken.

First, the Examiner is mistaken in stating that Saederup teaches that vMCK-2 exerts an effect on human CCR3-bearing cells. On page 10884, Saederup states that "only

human CCR3, a natural receptor for eotaxin, RANTES and MCP-3, was found to respond to MCK-1." Thus, vMCK-1, and not vMCK-2, was shown to exert an effect on human cells.

Second, the Examiner merely presumes that vMCK-1 and vMCK-2 have the same chemoattractant activity, based on the fact that the N-terminal chemokine domains of vMCK-1 and vMCK-2 are identical. However, given the lack of structural or functional characterization of the C-terminal domain of vMCK-2, it would not have been possible to predict its effect on the N-terminal chemokine domain. It would have been imprudent for the skilled artisan to presume that the large C-terminal extension of vMCK-2 would not affect the N-terminal chemokine receptor binding domain. In the absence of actual data, the skilled artisan in the field of chemokines would not have presumed that vMCK-1 and vMCK-2 are interchangeable, and would have required further experimentation before so concluding.

Given the uncertainty regarding the similarity between vMCK-1 and vMCK-2, it would have been unreasonable to expect that mouse viral vMCK-2 would exert chemoattractant activity in primates. Applicants' finding that vMCK-2 could nonetheless induce and augment an immune response in primates was unexpected and particularly surprising because there is no homolog of MCK-2 produced by a virus that infects humans.

Although the instant product claims are not limited by an intended use in humans, as discussed above it is entirely proper for the Examiner to consider the advantages of an invention when evaluating its obviousness. Here, the presently claimed pharmaceutical compositions comprising vMCK-2 and a tumor antigen may be used for vaccine administration to humans. The suitability of the composition to administer to a human is an inherent property of the composition irrespective of whether it is actually administered to a human. This advantage naturally follows from what is claimed, and it is entirely appropriate to consider it as evidence of nonobviousness.

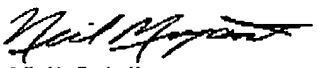
The proposed manner of combination of references, which requires that the skilled artisan recognize that a cytokine can be replaced by a specific chemokine, vMCK-2, and

reasonably believe in the interchangeability of vMCK-1 and vMCK-2 without any data, in the absence of any teaching or suggestion that the subgenus of chemokines were considered to be equally useful as the specified cytokines in cancer immunotherapy, appears to be the result of impermissible hindsight.

Based on the foregoing, Applicants respectfully request that the rejection of claims 69-72, 79-92 and 97-106 as being unpatentable over Kedar in view of Bystryn and Saederup be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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